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The first description of metyrapone use in severe Cushing Syndrome due to ectopic ACTH secretion in an infant with immature sacrococcygeal teratoma

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Abstract

Cushing syndrome due to ectopic secretion of ACTH in infants is rare. The treatment of choice is radical resection of the tumour in combination with pre-operative chemotherapy using steroidogenesis inhibitors if necessary. If radical surgery is not possible, palliative treatment of hypercortisolemia is recommended. The most frequently used drug in infants is ketoconazole. Experience with the use of metyrapone is poor. We report an 8-month-old female infant with congenital immature sacrococcygeal teratoma secreting AFP, beta hCG and ACTH who had undergone non-radical resection of the tumour mass and was receiving standard risk chemotherapy (vinblastine, bleomycin, and cisplatin). The infant initially presented at the age of 6 months with ACTH-dependent Cushing syndrome (cortisol and ACTH level 325 ng/mL, 112 pg/mL respectively). Treatment with ketoconazole was initiated with a dose of 600 mg/day. Due to its ineffectiveness metyrapne was added in increasing dosages, up to 1,500 mg/day. In addition the schema of chemotherapy was changed (adriamycin, bleomycin, carboplatin), which resulted in normalization of cortisol levels and blood pressure. There were no metyrapone side effects during the treatment period. We can conclude that treatment with metyrapone at a dose of 1500 mg/day might be effective and safe in infants with Cushing syndrome.

INTRODUCTION

Cushing syndrome (CS) due to ectopic secretion of ACTH in infants is extremely rare and challenging to treat. The treatment of choice is radical resection of the ACTH secreting tumour with pre-operative pharmacological inhibition of steroidogenesis and chemotherapy if necessary. If radical surgery is not possible, palliative treatment of hypercortisolemia is recommended. Inhibitors of steroidogenesis are difficult to use in this age group because data regarding effective dosage regimens is poor and there is no evidence of long-term safety and efficacy (Traina *et al.* 2013; Salunke *et al.* 2010). The most frequently used agent is ketoconazole. Experience with the use

CASE REPORT

of metyrapone in that age group is poor (Garge *et al.* 2013). We report a case of a female infant with severe Cushing syndrome due to ectopic ACTH secretion by an immature sacrococcygeal teratoma. This is the first description of metyrapone use in severe CS due to ectopic ACTH secretion in an infant.

CASE REPORT

A 8-month-old female infant was referred to the endocrinologist due to ACTH dependent CS. The patient was born at term to a G2 P2 mother by cesarean section with a birth weight of 4,280 g. The physical examine revealed anal atresia and a large tumour mass in the sacrococcygeal and pelvic region. Additional laboratory testing in the first days of life revealed a significant increase in alfafetoprotein (AFP) levels (59,000 ng/mL). At the age of 1 week, non radical resection of the tumor and the implantation of a colostomy were performed. The histopathological examination revealed a grade 3 immature teratoma. After surgery AFP levels returned to normal but a CT scan confirmed residual tumour mass (27×21×28 mm).

At the age of two months an increase in AFP and beta human chorionic gonadotropin (bata HCG) (379.5 ng/mL and 192 IU/L respectively) accompanied by an increase in tumour mass were found. Standard risk chemotherapy VBP (vinblastine, bleomycin, and cisplatin) was introduced. After 3 blocks of chemotherapy there was no regression in tumor mass diameters. At the age of 4 months a rapid increase in appetite and subsequent body weight were noticed accompanied by a systematic increase in blood pressure.

At the age of 6 months blood tests revealed elevated levels of cortisol and ACTH (325 ng/mL, 112 pg/mL respectively). The schema of chemotherapy was upgraded to high risk VIP (high risk etosposid, ifosfamid, cisplatin), but there was still no regression in tumor mass and cortisol levels were increasing gradually up to 627 ng/mL Ketoconazole was introduced at the initial daily dose of 400 mg. Despite intensive hypertensive treatment (metoprolol, captopril, aldacton), blood pressure was continuously increasing. The patient developed a hypertensive crisis with seizures and blood pressure at a maximum value of 210/160 mmHg.

On admission to the Children's University Hospital in Kraków at the age of 8 months, she presented in good general condition, with a body weight of 9 kg and blood pressure of 120/70 mmHg. Blood cortisol levels were high (739.8 ng/mL). The dosage of ketoconazole was increased to 600 mg without any significant effect on cortisol levels (699 ng/mL). At this point we decided to introduce metyrapone (125 mg twice a day). After 4 days of treatment, cortisol levels returned to within the normal range (172 ng/mL). After four days of stabilility, a rapid increase in cortisol levels up to 700 ng/mL was found. Metyrapone was gradually increased to the maximum dose of 250 mg every 4 hours (1,500 mg per day). In addition, second line chemotherapy was introduced (ABK protocol: adriamycin, bleomycin, carboplatin). After 4 days of such treatment cortisol levels decreased to 132 ng/mL and remained stable. Appetite decreased as well and there was no increase in body weight. Blood pressure was normal (90/57 mmHg). During the whole treatment period we did not observe any metyrapone side effects.

DISCUSSION

Ectopic secretion of ACTH by an immature teratoma is rare. There is one description of ACTH dependent CS due to immature sacrococcygeal teratoma in an adult female and one due to congenital immature teratoma in the region of the pituitary gland in an infant (Salunke *et al.* 2010; Moreno-Fernández *et al.* 2008). In the second case hypercortisolemia was successfully treated with ketoconazole at a dose of 200mg/day prior to the surgery (Salunke *et al.* 2010). On the contrary in this case a dose of 600 mg/day was not effective in the treatment of hypercortisolemia.

For this reason we decided to use metyrapone as second line therapy. Metyrapone is an inhibitor of endogenous adrenal corticosteroid synthesis. It inhibits the enzyme responsible for the 11β-hydroxylation stage in the biosynthesis of cortisol and to a lesser extent, aldosterone. The major potential side effects reported in adult patients are hirsutism, acne and mineralocorticoid effects (hypertension, hypokalemia and edema) (Feelders *et al.* 2010).

An additional problem in pediatric patients is the dosage, because commercially available capsules contain 250 mg of metyrapone and are not divisible. Metyrapone is occasionally used for short-term treatment of CS prior to surgery. Its efficacy in adults in the reduction of cortisol levels is about 75% (Traina *et al.* 2013; Feelders *et al.* 2010).

Ketoconazole is an antifungal agent that, in higher dosages, reduces adrenal steroid production via inhibition of multiple steroidogenic enzymes. Data from retrospective studies in adults show, that ketoconazole in a dose range between 400 and 1,200 mg/day can decrease cortisol production in about 70% of patients with CS (Feelders *et al.* 2010).

There is no data regarding the efficacy of these this drug in infants, however it is the most frequently used inhibitor of steroidogenesis in this age group (Dutta *et al.* 2012) In the presented case the dose of 250 mg/day was initially effective, but after a short amount of time, cortisol levels increased and an increase of the dose up to 1,500 mg/day was needed.

In addition second line chemotherapy was introduced as well (ABK protocol adriamycin, bleomycin, carboplatin). The result was a decrease in cortisol levels to 94.2 ng/mL This is the first description of metyrapone treatment in an infant with CS due to ectopic secretion of ACTH. During the whole treatment period with

increasing doses of metyrapone (up to 1,500 mg daily) and regular monitoring of cortisol levels and blood pressure, no side effects of the drug were observed.

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